

Nucleic Acid Testing for HIV-1 Diagnosis and Monitoring

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1. Introduction

In the test and treat era of HIV-1 epidemics, it is becoming extremely urgent to detect HIV-1 infected individuals. It is well known that HIV-1 testing enables health care professions to strategize interventions towards interruption of HIV-1 transmission chains, and to implement antiretroviral therapy. Expanding the number of persons treated with antiretroviral potentially decrease the number of new infections.[1] It is very well determined that the available antibodies based assays are very effective in the majority of cases to detect and confirm HIV-1 infection. However, some exceptions do apply. Diagnosis of HIV-1 infection during the so-called immunologic window period, which is the time between the acquisition of HIV infection and the HIV antibody detection, may be of fundamental importance in some specific cases. It has been debated that effective antiretroviral treatment instituted during acute infection period, which occurs during the immunologic window period, may contribute to a better restructuring of the host immune system, thus allowing to a better long term virologic control or to slower pace of disease progression.[2] Detection of infections during the immunologic window period is also a necessity in order to increase the safety of the blood supply. Furthermore, detection of HIV-1 infection is not specific enough in the cases where the passive transfer of antibodies occurs, such as among infants born from HIV infected mothers. For all these above applications, the direct identification of the pathogen can be an extremely helpful tool, which can be performed using molecular biology based techniques. It is important to bear in mind that passive transfer of antibodies do not occur exclusively among infant born from HIV positive mothers. In one case, a blood recipient from a seropositive unit did not get infected by HIV, but received antibodies that made anti HIV-EIA and Western-blot positive for a period up to six month, being the western blot profile identical to the one found in the infected blood donor.[3] Other case also showed the immediate detection of donors anti-HIV antibodies following a health care work accident, where a broken blood collection tube injured a nurse.[4]

Molecular based techniques area also present in the HIV monitoring tools in tests known as viral load assays. Viral load monitoring can classically predict the pace of HIV-1 disease progression[5] and the effectiveness of antiretroviral treatment. Those tests are still evolving

and becoming more sensitive, since detection of low level residual replication is becoming increasingly important in the management of HIV-1 infected individuals. Furthermore, molecular biology has been applied as a valuable tool in detection of HIV strains resistant to antiretrovirals. It is no longer acceptable empirical change in antiretroviral treatment since resistance testing can increase the odds of a successful salvage therapy.[6, 7] As treatment evolves, laboratory tests emerge to make any kind of treatment more effective, safe and predictable. It is the pharmacogenomics playing its role, and again, based in molecular biology techniques. This chapter will describe the challenges related to HIV diagnosis and monitoring, and the contribution of molecular tests in this field.

2. Nucleic acid testing and diagnosis of primary HIV infection

a. Early stages of HIV Infection

After an exposure to HIV-1, and in spite of the exposition route, a dendritic cell will capture the virus and conduct it to the regional lymphonode with the intention of constructing the adaptative immune response.[8] Odds of becoming HIV infected relates to the viral load of the donor of the infection in spite of the rout of HIV transmission. Studies show that there is a threshold level of viral load bellow which heterosexual transmission is unlikely to occur.[9, 10] The level of viremia in a blood donor at the time of the donation is the primary factor influencing the probability of the infection.[11] A similar relationship between viral load and HIV transmission has been proposed for perinatal and[12] needlestick exposures.[13, 14] Interestingly however, HIV-1 transmission is considered to be clonal in the large majority of the cases, since 76% start from a single transmitted HIV strains and in 24% of the cases, transmission is seeded by two to five HIV strains.[15] The burst of viremia will start after the dendritic cells reach the regional lymphonode, which takes from 5 to 14 days.[16] Dendridic cells do not get infected by HIV, and after attachment to the DC-SIGN, these cells captures the virus and bring it trapped in its surface or even protected by endocytosis in its way to the regional lymphonode (the dendritic cell present in the genital mucosa is the Langherhan cell). The time elapsed between HIV exposure and the burst of viremia is denominated eclipse period.[17]

When viral replication starts, HIV-1 viral load tends to be exceedingly high, usually with the detection of more than 1 million of HIV RNA copies/mL.[17] Once host immune specific humoral and cellular immunity starts to emerge, viral load tends to decrease to basal values which tend to be constant for the rest for life, and usually affected only by antiretroviral treatment.

Third generation HIV EIA tests can detected HIV as early as 1 month after exposure, and time elapsed between the exposure to HIV and detection of specific antibodies are described as the immunologic window period (Figure 1). The first HIV marker that can be detected is the RNA of virions, which occurs after 17 days (13 to 28), followed by the proviral DNA at the 20th day (18 to 34), followed by the detection of the p24 antigen, which occurs at day 22 (18 to 34).[17] All those markers can be readily used to shorten up the period to detect HIV-1 infection after the exposure event.

b. Nucleic acid testing during the immunologic window period.

The diagnosis of HIV infection is challenging in individuals with recent exposure or symptomatic primary infection, and or the detection of HIV infection from mother to child

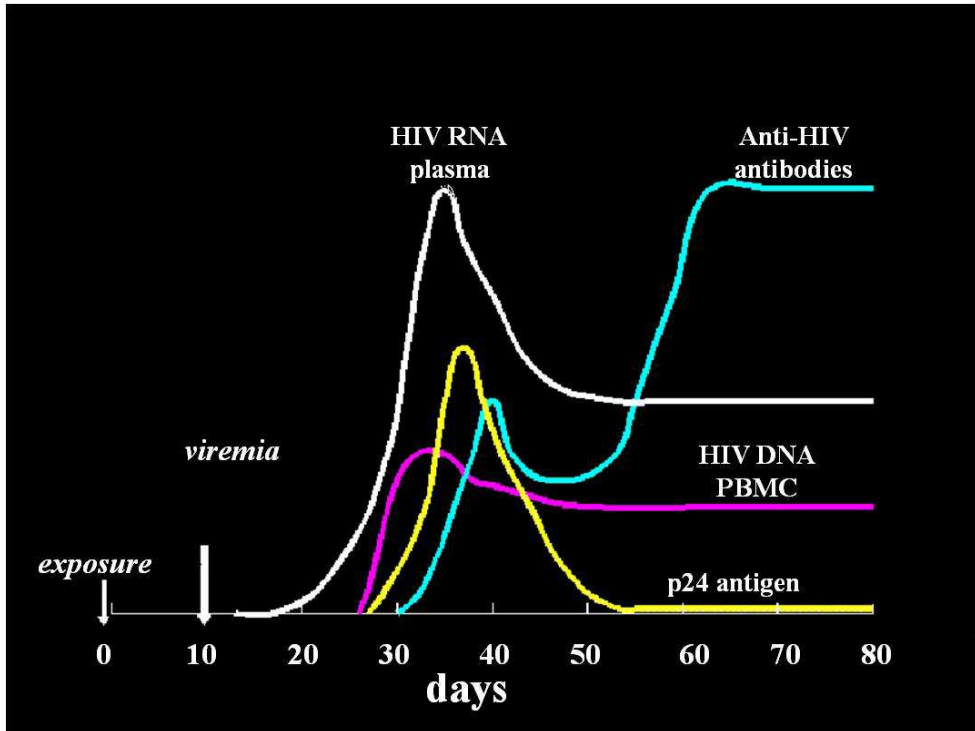


Fig. 1. Approximately sequence and time course of virological and serological events during primary HIV-1 infection. Plasma HIV-1 RNA is detected by commercial viral load assays, whereas HIV DNA in PBMCs is detected by home brew PCE assays.[17]

after vertical exposure. Either of the above mentioned tests, the virion RNA, proviral DNA and p24 antigen can be of utility in the detection of HIV infection after the eclipse period and before fully HIV-1 seroconversion. Especially challenging is the diagnosis among children born from infected mothers. All those children will receive a passive transfer of maternal antibodies which can make anti HIV results positive for up to 18 months after delivery.[18] It is known that the great majority of exposed children will not become HIV infected. Without any sort of antiretroviral prophylaxis, which include the treatment of the mother and use of antiretrovirals by the exposed children for a limited time period, only 20 to 30% of exposed children will become infected.[19] Incident infections will follow to 7% with the use of zidovudine monotherapy by the mothers,[18] being even 50% more efficacious with the use of single doses nevirapine by the time of delivery[20] and to virtually zero if highly active antiretroviral therapy is successfully used, and maintaining maternal viral loads below detection limits. Therefore, efforts to overcome the problem of low specificity in diagnosing HIV infection in newborns have been made targeting the direct identification of the virus. The first attempts to overcome this diagnostic problem have been made with the use of co-culture to detect HIV among newborns,[21] which is cumbersome, expensive, takes longer time, and requires well equipped laboratories that cannot be used in large scale in the clinical setting. Therefore, detection of HIV DNA and RNA seems to be more appropriate to detect the vertical transmission of HIV-1.

Timing of vertical HIV transmission is also important in the strategy to test children born from infected mothers. A smaller and variable proportion of HIV transmission will occur intra-uterus (around 30%), and in these cases, newborns will likely be viremic by the time of birth.[22] In the peripartum transmission, however, the presence of viruses will occur in general around two weeks after birth.[23] Other feature that needs to be taken into account relates to the viral dynamics of HIV- replication among children infected by the vertical route. Whereas among adults, viral load in general reaches the set point by 6 months after HIV infection,[24] and mean basal viral load is inferior to 100,000 RNA copies/mL, children will take much longer to show a week control of viremia after primary infection.[25] In the case of infants, viral loads will be in general above 100,000 RNA copies/mL for a period that is superior to 24 months.[25]

The use of RNA rather than proviral DNA for detection of primary infection has the advantage of providing a shorter window period between HIV acquisition and the first detectable virologic marker, as seen in Figure 1. False positive results with qualitative DNA PCR or quantitative RNA methodologies have been reported in the literature.[26-28] Usually the false positive result can be attributed to the Polymerase Chain reaction (PCR) carry over, decreasing specificity to as low as 96%.[26] As an interesting example, transient HIV-1 infection has been proposed based on the detection of a positive PCR among children who seroreverted (HIV uninfected children born from HIV positive mothers who lose antibodies after 18 months of life).[29] In these cases, detection of human HIV-1 on only one or a few occasions in these infants has been interpreted to indicate that infection may be transient rather than persistent. However, genetic analysis of viruses revealed that either specimens were mistakenly attributed to an infant, or phylogenetic analysis failed to demonstrate the expected linkage between the infant's and the mother's virus,[30] being PCR carry-over the likely explanation for these mistakes.

PCR-carry over, which is a feature of molecular based tests that amplify nucleic acid targets, can be more difficult to be detected in qualitative rather than quantitative assays. In this

sense, viral load assays for detecting primary infection has the advantage of potentially discriminating false positive results due to PCR carry over from true positive results since it is expected a high viral load in these situations, being this particularly true for children born from infected mother. In other words, a qualitative assay gives a “yes” or “no” result, whereas the viral load assays can potentially discriminate false positive results since it is expected a very high viral load during primary HIV infection or in infection among children with less than two years old. It has to be taken into account that PCR carry over will always provide a considerable low viral load, which usually is low than 1,000 RNA copies/mL. Therefore, as discussed above, better tests to detect HIV infection in these target populations are assays that targets RNA rather than DNA, and have the quantitative nature rather than qualitative, those tests being the RNA viral load assays. When those tests are performed in children using samples collected after 3 weeks of deliver, the sensitivity, specificity, positive and negative predictive value can be all 100%. [23]

c. HIV-1 RNA quantitation for HIV-1 infection monitoring (ultra-sensitive)

It has been defined since the beginning of the HIV epidemics that HIV-1 viral replication relates well with disease progression and response to treatment.[5] The guidelines for HIV treatment recommend that viral load should be kept as low as possible, preferable bellow detection levels. However, questions have been always related to how sensitive should be a viral load assays. It has been demonstrated that viral replication will occur in spite of the apparently complete HIV suppression using antiretrovirals. One cohort of 130 treated patients kept of HIV-1 RNA viral load bellow 75 copies/mL revealed that 80% of individuals will still present detectable viremia when more sensitive viral load strategies were used (1 RNA copies/mL of plasma) being the median viral load equal 3.1 copies/mL.[31, 32] Other study showed that this low level viremia is likely to be shed by the gastrointestinal tract sanctuary.[33] It has been described that this low level (and sometimes unrecognized) viral replication may lead to a CD4 and CD8+ T cell activation which relates to apoptosis and disease progression.[34, 35] This cell activation can be also detected among elite suppressors, which are individuals that naturally control viremia thus preventing the CD4+ T cell decline, and this cell activation may relate to deleterious aspects among those individuals.[36, 37]

The risk of selecting HIV-1 antiretroviral resistant strains also relates to the level of viral replication, and the pace of emergence of resistant related mutations may be somewhat predictable. Indeed, the number of new mutations relates to the residual viral replication, being directly proportional to the viral load of individuals in virologic failure.[38]

d. HIV-1 antiretrovirals resistance testing

It has been recognized that HIV resistance testing is of benefit in the performance of salvage therapy[7, 31, 39-41] and survival rates.[42] Furthermore, resistant testing exerts great influence in medical decision regarding choice of antiretrovirals in salvage therapy.[43] The current available resistance testing are the so called genotypic resistance tests. Those are indirect measures of resistance, where HIV RNA is obtained, reverse transcribed and cDNA is sequenced to detect the antiretroviral related mutations. Interpretation algorithms are applied to infer the activity of diverse antiretroviral agents. The direct measure of resistance is provided by the phenotypic assays. In these assays, RNA from HIV is also purified and recombinant viruses that have the *pol* gene of patient's HIV and the backbone of a

laboratory virus are produced in vitro. These pseudoviruses are cultured with different concentrations of different antiretrovirals and the resistant related fold change is determined. Fold changes always refer to the amount of drug used to inhibit the patient's HIV compared to the wild type laboratory strain. Biological and clinical cut-offs are used to infer the probability of response to specific antiretrovirals. Genotypic tests are easier to perform, more available and less expensive than phenotypic based assays. They also are more sensitive in detecting resistance when mixtures of mutant and wild type viruses are present, since it is likely that resistant strains will be overwhelmed by the more fit wild type strains in the initial culture producing the pseudoviruses.[44] The quantitative nature of phenotypic based assays may be of utility in analyzing the highly resistance strains. Phenotypic tests are also advantageous for new antiretrovirals with poorly defined resistance profile and perhaps for non-B strains, where resistance pathways and mutations may not be yet available. Furthermore, the presence of fold change and clinical cut-off increase the confidence of physicians in the choice of salvage therapy.[43] There is also the virtual phenotype test, which is in fact a genotypic based assays. In these tests, HIV-1 *pol* sequences are submitted to a specific database, which will infer the phenotypic profile of viruses providing fold changes and clinical cut-offs. In fact, performance of virtual phenotype has been comparable or better than the performance found using phenotype for salvage therapy.[41, 45] The likely explanation for the alleged better performance of virtual phenotype as compared to the "real" phenotype relies in the fact that virtual phenotype will be less likely to underestimate resistance since mixtures of wild type and resistant strains found in the sequencing process will be considered as resistant. Conversely, as explained above, mixtures of wild type/resistant will facilitate overgrowth of wild type strains in cell culture.

e. HIV-1 Tropism

The practical issue of HIV-1 tropism emerged with the development of CCR5 antagonists as antiretrovirals. Nonetheless, HIV tropism has been studied for a long time in the attempt to correlate the HIV-1 coreceptor use with cytopathicity. In summary, HIV may use CCR5 and CXCR4 chemokine receptors for entry, and viruses that exclusively use the CCR5 are denominated R5, viruses that use CXCR4 are X4, whereas viruses able to use both coreceptors are dual tropic (reviewed by Moore et al).[16] Infection usually starts with R5 viruses and as HIV-1 quasispecies evolves, CXCR4 using strains may emerge. There is also the association between the emergence of CXCR4 using strains and rapid HIV-1 disease progression.[46] Therefore, it is conceivable that the determination and monitoring HIV-1 tropism over time may be of use in the decision of introduction of antiretroviral treatment or more frequent evaluation of CD4+ T cell levels in the infected patient.

The main utility of tropism determination relates to the decision of use of CCR5 antagonists such as maraviroc, since this specific class of antiretrovirals will lose activity in the presence of detectable X4 or dual tropic viruses.[47] Therefore, a tropism test before treatment with these drugs is required; gold standard tropism tests being the phenotypic based tests. One phenotypic tropism test constructs pseudoviruses containing the gp160 of patient's viruses and a backbone of HIV-1 laboratory virus plus the luciferase gene.[48] Two lineages of cells containing either the CCR5 or the CXCR4 coreceptors are used in two distinct lab reactions. Once infected, light will be generated from cells due the

presence of the luciferase gene, and HIV can be detected in the culture either inside cells harboring CCR5 and/or CXCR4 coreceptors. If HIV is detected only in the culture of cells harboring CCR5 coreceptor, viruses will be classified as R5, whereas X4 viruses will appear only in the culture of cells harboring CXCR4 coreceptors. In the case viruses are detected in both cultures, it is reported that dual mixed and/or mixtures of R5 and X4 are present. Alternatively, genotropism tests can be used. These tests detect substitutions at the V3 region of gp120 HIV-1 gene in order to predict the CXCR4 use by viruses present in the patient's quasispecies. Although phenotypic and genotypic tests do not fully agree with each other, genotypic tests are probably equally able to predict virologic treatment failure in maraviroc containing antiretroviral schemes[47] and have been advocated as preferential in some guidelines.[49]

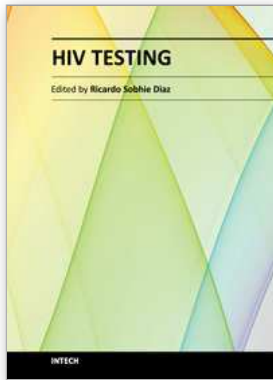
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HIV Testing

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ISBN 978-953-307-871-7

Hard cover, 132 pages

Publisher InTech

Published online 18, January, 2012

Published in print edition January, 2012

It can be said that now is the best time for everyone infected to become aware of their own HIV status. The state of the art in HIV management progressively reveals that antiretroviral treatment can prevent transmission, as well as chronic damage in the human body, if started early. Unfortunately, antiretrovirals are not widely available in many places, especially in developing countries. In these parts of the world, diagnosis of HIV infection must be kept in the agenda as a priority, in order to understand specific details of local epidemics and as an effort to interrupt the chain of HIV transmission.

How to reference

In order to correctly reference this scholarly work, feel free to copy and paste the following:

Ricardo Sobhie Diaz (2012). Nucleic Acid Testing for HIV-1 Diagnosis and Monitoring, HIV Testing, Prof. Ricardo Diaz (Ed.), ISBN: 978-953-307-871-7, InTech, Available from: <http://www.intechopen.com/books/hiv-testing/nucleic-acid-testing-for-hiv-1-diagnosis-and-monitoring>

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